7. (Amended) A method of treating the interleukin-12-induced inflammatory response of an inflammatory bowel disease in a human subject, comprising administering to a subject an amount of a ligand of complement receptor 3 or complement receptor 4 effective in downregulating production of interleukin-12, thereby treating the interleukin-12-induced inflammatory response of an inflammatory bowel disease, wherein the ligand is not an antibody having the myelomonocytic recruitment inhibitory activity of monoclonal antibody 5C6.

10. (Amended) The method of claim 1, 2, 3, 4, 5, 6, 7 or 8, wherein the ligand of complement receptor 3 is selected from the group consisting of antibodies to complement receptor 3 which do not have the myelomonocytic recruitment inhibitory activity of monoclonal antibody 5C6, iC3b, ICAM-1, fibrinogen, β-glucan, C3b, ICAM-2, ICAM-3, a complement receptor 3-binding microorganism and a complement receptor 3-binding product of a complement receptor 3-binding microorganism.

REMARKS

Claims 1-8 and 10 are pending in the present application. Claims 1-3, 5, 7 and 10 are amended herein for clarity and to more particularly define the invention. Support for these amendments can be found throughout the specification and as described below. No new matter is believed to be added by these amendments. In light of these amendments and the following remarks, applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

Applicants appreciate the opportunity to personally interview this case on July 31, 2001 with Examiners DeCloux and Saunders. The following remarks more specifically address the issues discussed in the interview, as well as other issues regarding the pending claims.

I. Rejection Under 35 U.S.C. § 112, second paragraph

The Office Action states that claim 10 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, claim 10 is allegedly indefinite because it depends from canceled claim 9.

Claim 10 is amended herein to no longer depend from canceled claim 9. Thus, applicants believe this rejection has been overcome and respectfully request its withdrawal.

II. Rejection Under 35 U.S.C. § 102(e)

The Office Action states that claims 1-8 and 10 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Karp et al. (U.S. Patent No. 6,086,876; issued July 11, 2000), filed February 6, 1998, which has priority to February 7, 1997.

Applicants assert that the claimed invention was conceived and reduced to practice prior to the February 7, 1997 priority date of U.S. Patent No. 6,086,876. Specifically, applicants provide herewith as Exhibit I, a Declaration under 37 C.F.R. § 1.131 (an unsigned copy is enclosed; a signed copy of the Declaration will be submitted shortly) of Drs. Brian Kelsall, Warren Strober, Thomas Marth and Ivan Fuss, wherein they declare that prior to February 7, 1997, they conceived and reduced the claimed invention to practice in the United States of America.

In particular, the Declaration states that the co-inventors conceived and reduced the invention to practice in the Mucosal Immunity Section of the Laboratory for Clinical Investigation of the National Institute for Allergy and Infectious Diseases of the National Institutes of Health, USA, as shown in Exhibits A and B, attached to the Declaration.

Specifically, Exhibit A is an abstract that was submitted to the American Association of Immunology prior to February 7, 1997. This abstract describes experiments conducted in the co-inventors' laboratories and data from these studies which demonstrate the downregulation of IL-12 production by administration of a ligand of CR3 in an animal model of septic shock.

Exhibit B is a three-page set from the laboratory notebook of Dr. Ivan Fuss that describes data from experiments conducted in the co-inventors' laboratories prior to February 7, 1997, which demonstrate the downregulation of IL-12 production by administration of a ligand of CR3 in an animal model of autoimmune disease.

Therefore, the evidence set forth in the present Declaration demonstrates that the claimed invention was conceived and reduced to practice prior to the February 7, 1997 priority date of U.S. Patent No. 6,086,876. Thus, the Karp et al. reference (U.S. Patent No. 6,086,876) is not available as prior art in a rejection of the claims of the present invention under 35 U.S.C. § 102(e). Therefore, applicants believe this rejection has been rendered moot and respectfully request its withdrawal.

III. Rejection Under 35 U.S.C. § 102(b)

The Office Actions states that claims 1-8 and 10 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Rosen et al. (WO 89/04174, published May 18, 1989). Further

stated in the Office Action is that Rosen et al. teaches a method of administering an antibody with specificity for CR3 for the treatment or prophylaxis of inflammatory autoimmune and hypersensitivity diseases, and in particular inflammatory bowel disease, and consequently its symptoms, as recited in the instant claims. The Office Action goes on to state that although the referenced teachings do not explicitly teach that administration of antibodies directed to CR3 downregulates interleukin-12 in a subject or treats an interleukin-12 induced inflammatory response, down regulation of interleukin-12 in a subject and treatment of an interleukin-12-induced inflammatory response would be inherent properties effected by administration of antibodies against CR3. Therefore, according to the Office Action, the referenced teachings anticipate the claimed invention.

Claims 1-3, 5, 7 and 10 are amended herein to recite that the ligand of this invention is not an antibody having the myelomonocytic recruitment inhibitory activity of monoclonal antibody 5C6. Support for this amendment can be found throughout the specification and for example, on page 22, lines 27-28, where it is stated that "BALB/c mice were given intraperitoneal injections of either CR3 antibodies (1 mg of clone M1/70 or 0.5 mg of 5C6, both of which are non-opsonizing antibodies (8, 32))."

Further support for this amendment can be found in references 8, 11 and 13 (as cited on page 2, lines 1-7, on page 23, line 3 and on page 24, line 15, and as listed with titles in the reference section of the specification on page 27), entitled "Role of CR3 in induced myelomonocytic recruitment: Insights from *in vivo* monoclonal antibody studies in the mouse;" "Antibody to the murine type 3 complement receptor inhibits T lymphocyte-dependent recruitment of myelomonocytic cells in vivo;" and "Exacerbation of murine listeriosis by a monoclonal antibody specific for the type 3 complement receptor of myelomonocytic cells," respectively.

Therefore, as amended herein, claims 1-3, 5, 7 and 10 are directed to an invention that is not disclosed or suggested in the Rosen et al. publication. Specifically, the disclosure in Rosen et al. is directed to a subgenus of antibodies which bind CR3 and have the specific effect of inhibiting myelomonocytic recruitment to inflammatory sites *in vivo*. It is further stated in Rosen et al. that not all antibodies which bind CR3 have this activity. See, e.g., page 3, third full paragraph, wherein it is stated that monoclonal antibodies M1/70 and 44 were shown not to exhibit this activity. Monoclonal antibodies M1/70 and 44 have been shown in the present invention to have IL-12 downregulating activity (see Table 1), thereby identifying members of a distinct subgenus of antibodies to CR3 having IL-12 downregulating activity which are not disclosed in the Rosen et al. reference. Therefore, Rosen et al. fails to disclose each feature of what applicants claim as their invention and this reference does not anticipate the present invention. Thus, applicants believe this rejection has been overcome and respectfully request its withdrawal.

Negative limitation

As set forth above, it is applicants' position that there is sufficient support in the specification to include in the claims the limitation that the ligand of this invention is not an antibody having the myelomonocytic recruitment inhibitory activity of monoclonal antibody 5C6. In particular, applicants explicitly recite monoclonal antibody 5C6 in the specification as a specific example of a member of the subgenus carved out of the claims by this limitation and have included several references (in particular, references 8, 11 and 13), the disclosures of which are incorporated by reference in their entireties as stated on page 25, lines 24-27 of the specification, to describe the subgenus of antibodies having the myelomonocytic recruitment inhibitory activity of 5C6. Thus, applicants adequately describe and support a subgenus of antibodies that have the myelomonocytic recruitment inhibitory activity 5C6 in the specification. Therefore, by amending the claim to include a limitation that the ligand of this invention is not an antibody having the myelomonocytic recruitment inhibitory activity of monoclonal antibody

5C6, applicants are merely claiming less than the full scope of their disclosure, which has precedent in the patent case law. See e.g., In re Johnson and Farnham, 558 F. 2d 1008, 194 USPQ 187 (CCPA 1977). (copy enclosed).

It is also applicants' position that the entire subject matter of references 8, 11 and 13 of the specification is properly included in the present specification by incorporation. Specifically, applicants note that both the meaning and intent of "incorporation by reference" are well supported in the case law. See, e.g., In re Lund, 376 F. 2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). ("As the expression itself implies, the purpose of 'incorporation by reference' is to make one document become a part of another document by referring to the former in the latter in such a manner that it is apparent that the cited document is part of the referencing document as if it were fully set out therein."). See also Interstate Consol. St. Ry. V. Massachusetts, 297 U.S. 79, 84 (1907). ("If the charter, instead of writing out the requirements of Rev. Laws, 112, § 72, referred specifically to another document expressing them, and purported to incorporate it, of course the charter would have the same effect as if it itself contained the words."). See also In re Howarth, 654 F. 2d 103, 106, 210 USPQ 689, 692 (CCPA 1981). ("After ruling that prior U.S. patents may be so incorporated, In re Stauber, 18 CCPA 774, 45 F.2d 661, 7 USPQ 258 (1930), this court extended the doctrine of incorporation by reference stating as a general guideline in In re Heritage, 37 CCPA 1109, 1115, 182 F.2d 639, 643, 86 USPQ 160, 164 (1950), that 'any reference to a disclosure which is available to the public is permissible.'"). (A copy of each of these cases is enclosed.)

Therefore, applicants assert that all of the references cited in the application are incorporated in their entireties by reference, as stated on page 25, lines 24-27 of the specification and are part of the specification as if they were fully set out therein. Thus, applicants believe that the description of monoclonal antibody 5C6 in the specification, combined with the disclosures

set forth in references 8, 11 and 13, which are also part of the specification via incorporation by reference, provide adequate support for the claim amendments set forth herein.

Furthermore, as set forth above, although applicants believe that the case law adequately supports their position that the specification includes all of the subject matter of references 8, 11 and 13, by incorporation by reference, applicants also provide herewith a copy of Atmel Corporation v. Information Storage Devices, Inc., 198 F. 3d 1374, 53 USPQ 2.d 1225 (Fed. Cir. 1999), in support of the proposition that the title of a reference, when recited in the specification, is considered part of the disclosure of the invention. On this basis, the titles of references 8, 11 and 13, as provided on page 27 of the specification, are of themselves sufficient to adequately support a claim amendment reciting that the ligand of this invention is not an antibody having the myelomonocytic recruitment inhibitory activity of monoclonal antibody 5C6. Thus, for these additional reasons, applicants believe this rejection has been overcome and respectfully request its withdrawal and allowance of the pending claims to issue.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of the application to issue.

IV. Supplemental Information Disclosure Statement

As discussed during the July 31, 2001 interview, applicants will be submitting a Supplemental Information Disclosure Statement (IDS) along with the submission of the executed Declaration Under 37 C.F.R. § 1.131.

A check in the amount of $390.00 (extension of time fee) and a Request for Extension of Time are included herewith. This amount is believed to be correct. However, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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Certificate of Mailing

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date shown below.

Mary L. Miller — August 7, 2001
Mary L. Miller — Date

Marked up version of amended claims and all pending claims

1. A method of downregulating interleukin-12 production in a subject, comprising administering to the subject an interleukin-12 downregulating amount of a ligand of complement receptor 3 or complement receptor 4 effective in downregulating interleukin-12 production, wherein the ligand is not an antibody having the myelomonocytic recruitment inhibitory activity of monoclonal antibody 5C6.

2. A method of reducing an interleukin-12-induced inflammatory response in a subject, comprising administering to the subject an amount of a ligand of complement receptor 3 or complement receptor 4 effective in reducing the interleukin-12-induced inflammatory response, wherein the ligand is not an antibody having the myelomonocytic recruitment inhibitory activity of monoclonal antibody 5C6.

3. A method of reducing the symptoms characteristic of an autoimmune disease by downregulating interleukin-12 production, comprising administering to the subject an amount of a ligand of complement receptor 3 or complement receptor 4 effective in downregulating interleukin-12 production, thereby reducing the symptoms characteristic of an autoimmune disease, wherein the ligand is not an antibody having the myelomonocytic recruitment inhibitory activity of monoclonal antibody 5C6.

5. A method of treating the interleukin-12-induced inflammatory response of an autoimmune disease in a human subject, comprising administering to a subject an amount of a ligand of complement receptor 3 or complement receptor 4 effective in downregulating production of interleukin-12, thereby treating the interleukin-12-induced inflammatory response of an autoimmune disease, wherein the ligand is not an antibody having the myelomonocytic recruitment inhibitory activity of monoclonal antibody 5C6,.

6. The method of claim 5, wherein the autoimmune disease is selected from the group consisting of inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, diabetes mellitus, pernicious anemia, autoimmune gastritis, psoriasis, Bechet's disease, idiopathic thrombocytopenic purpura, Wegener's granulomatosis, autoimmune thyroiditis, autoimmune oophoritis, bullous pemphigoid, pemphigus, polyendocrinopathies, Still's disease, Lambert-Eaton myasthenia syndrome, myasthenia gravis, Goodposture's syndrome, autoimmune orchitis, autoimmune uveitis, systemic lupus erythematosus, Sjogren's syndrome and ankylosing spondylitis.

7. A method of treating the interleukin-12-induced inflammatory response of an inflammatory bowel disease in a human subject, comprising administering to a subject an amount of a ligand of complement receptor 3 or complement receptor 4 effective in downregulating production of interleukin-12, thereby treating the interleukin-12-induced inflammatory response of an inflammatory bowel disease, wherein the ligand is not an antibody having the myelomonocytic recruitment inhibitory activity of monoclonal antibody 5C6.

8. The method of claim 7, wherein the inflammatory bowel disease is selected from the group consisting of Crohn's disease, ulcerative colitis and celiac disease/tropical sprue.

10. The method of claim 1, 2, 3, 4, 5, 6, 7 or 8, wherein the ligand of complement receptor 3 is selected from the group consisting of antibodies to complement receptor 3 which do not have the myelomonocytic recruitment activity of monoclonal antibody 5C6, iC3b, ICAM-1, fibrinogen, β-glucan, C3b, ICAM-2, ICAM-3, a complement receptor 3-binding microorganism and a complement receptor 3-binding product of a complement receptor 3-binding microorganism.